DEGENERATIVE LESIONS OF A CORONARY CHEMORECEPTOR AND NEARBY NEURAL ELEMENTS IN THE HEARTS OF VICTIMS OF SUDDEN DEATH*,**

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Within the adhesive juxtaposition of the proximal portions of the human arota and main pulmonary artery there are a number of complex neural elements which include myelinated and unmyelinated nerves, ganglia and special neuroreceptors (1–5). A chemoreceptor present in this location is rarely represented by a single small mass of glomoid tissue but more often is comprised of several separate units of variable size. Whether one or several, these glomera are nearly always supplied by a small branch of the main left coronary artery (4–7). There is an identical coronary chemoreceptor present in the heart of the dog, and canine experimental studies have demonstrated that it is maximally activated by 5-hydroxytryptamine (serotonin) to cause a virtual doubling of central aortic pressure within 4 to 6 seconds (5, 8, 9). The afferent neural pathway for this cardiogenic hypertensive chemoreflex courses in the vagus nerve (10) but the efferent pathways include both vagal and sympathetic neural participation (11, 12).

In addition to the abrupt hypertension which it causes, this cardiogenic chemoreflex concomitantly exerts a powerful and potentially unstabilizing influence upon several aspects of cardiac performance, including electrical activity (5, 9). Clinical evidence of such events observed in humans during either angina pectoris or acute myocardial infarction (especially the early phase) have long been familiar to experienced clinicians (13, 14) and were given the colorful description of "autonomic storms" by Sir Thomas Lewis (15). Although it was once suggested (16) that the origin of these autonomic storms must be from some then undefined intracardiac chemoreceptor, we (17) and others (18) have subsequently presented evidence to indicate that the origin in man is

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within the coronary chemoreceptor which is the special subject of the present study.

Hearts of victims of sudden unexpected death have been shown to exhibit a variety of inflammatory and degenerative lesions of intracardiac nerves and ganglia, abnormalities collectively termed cardioneuropathies (19). Since both experimental and clinical evidence cited above would lead one to suspect that similar morphological abnormalities of the coronary chemoreceptor might cause serious cardiac electrical instability, of a type which most believe underlies the majority of examples of sudden unexpected death, this study was undertaken to examine that chemoreceptor together with its neighboring neural elements taken from the hearts of victims of sudden death.

MATERIAL AND METHODS

Sixteen hearts available from an archival collection of sudden unexpected deaths were selected upon the basis of the appropriate area of the heart being intact and suitable for examination. All specimens were well preserved in neutral formalin. Ages ranged from childhood to middle adult life and there were approximately equal numbers of males (seven) and females (nine). All had died suddenly and unexpectedly with no noncardiac abnormalities found at autopsy. Except for a variety of abnormalities in the cardiac conduction system, there were no other recognized cardiac lesions to explain sudden death, and in particular no such lesions in the major coronary arteries, cardiac valves or working myocardium. No case in the study had any recognizable systemic disease such as diabetes mellitus or amyloidosis.

There are usually at least two and there may be as many as 6 or 8 small glomera which collectively comprise the chemoreceptor supplied by a small branch of the main left coronary artery. Even the larger units of this coronary chemoreceptor are rarely more than 1 mm in maximal dimensions. Since it is impossible to predict in any given heart how many such units may be present or where their exact location will be within the region between the aorta and main pulmonary artery, it is necessary to prepare serial sections of the entire area. The block which is removed for this purpose includes a few millimeters of left ventricular and septal myocardium located just below the origin of the two great vessels and then extends up to include the apposed aorta and main pulmonary artery for a distance of 3 to 4 cm. The main left coronary artery is routinely incorporated since the nutrient artery to the chemoreceptor virtually always originates from it. The entire block is embedded in paraffin and then cut serially in 8 micron sections, with each tenth section saved and each thirtieth stained for examination. The routine stain is a Goldner

trichrome but selected additional sections are prepared with other stains such as the periodic acid Schiff, Verhoeff-van Gieson elastic, or Gomori methenamine silver (or other silver impregnation methods). For each case in the present study approximately 150 slides were examined with a light microscope.

RESULTS

Most of the easily recognized glomera stand alone, usually with a conspicuous central artery and numerous nearby nerves and ganglia. However, either small or large glomera are also sometimes found attached to or even incorporated within nerves or ganglia or a combination of both. Thus, there are occasional triple component structures containing a nerve and ganglion and glomus all together.

In eleven of the sixteen hearts there was extensive degeneration with associated inflammation in the coronary chemoreceptor, as well as within various adjacent nerves and ganglia (Figures 1–7). In two other of the sixteen hearts there were only small areas of focal inflammation or degeneration in some sections of the coronary chemoreceptor (Figure 5) and in the three remaining hearts the chemoreceptor appeared to be normal. However, in every one of the sixteen hearts there were scattered abnormalities among the nerves and ganglia of the region. In two of the sixteen hearts small aggregations of platelets were present within the coronary chemoreceptor's arterioles but there was no thrombotic occlusion.

Inflammation of nerves or ganglia in the heart differs from the histologic appearance of most examples of arteritis or valvulitis or myocarditis by usually being confined to the nerve or ganglion or extending only a very short distance into neighboring tissue. This same confining characteristic is true for the chemoreceptor tissue (glomera) as well. Whatever the etiology may be, it appears that it is relatively selective for these several neural structures in the heart.

DISCUSSION

Whenever the pathogenesis of sudden unexpected death is discussed, the coronary circulation is always considered, as would logically be expected since its disturbance can have profound effects upon cardiac stability. Although less often considered, neural control of the heart may be even more powerful in the moment-to-moment regulation of cardiac performance. In relation to the heart's electrical stability, neural influence can remarkably alter the rate or nature of cardiac rhythm, the speed of AV (atrioventricular) conduction and possibly its exact route, and the

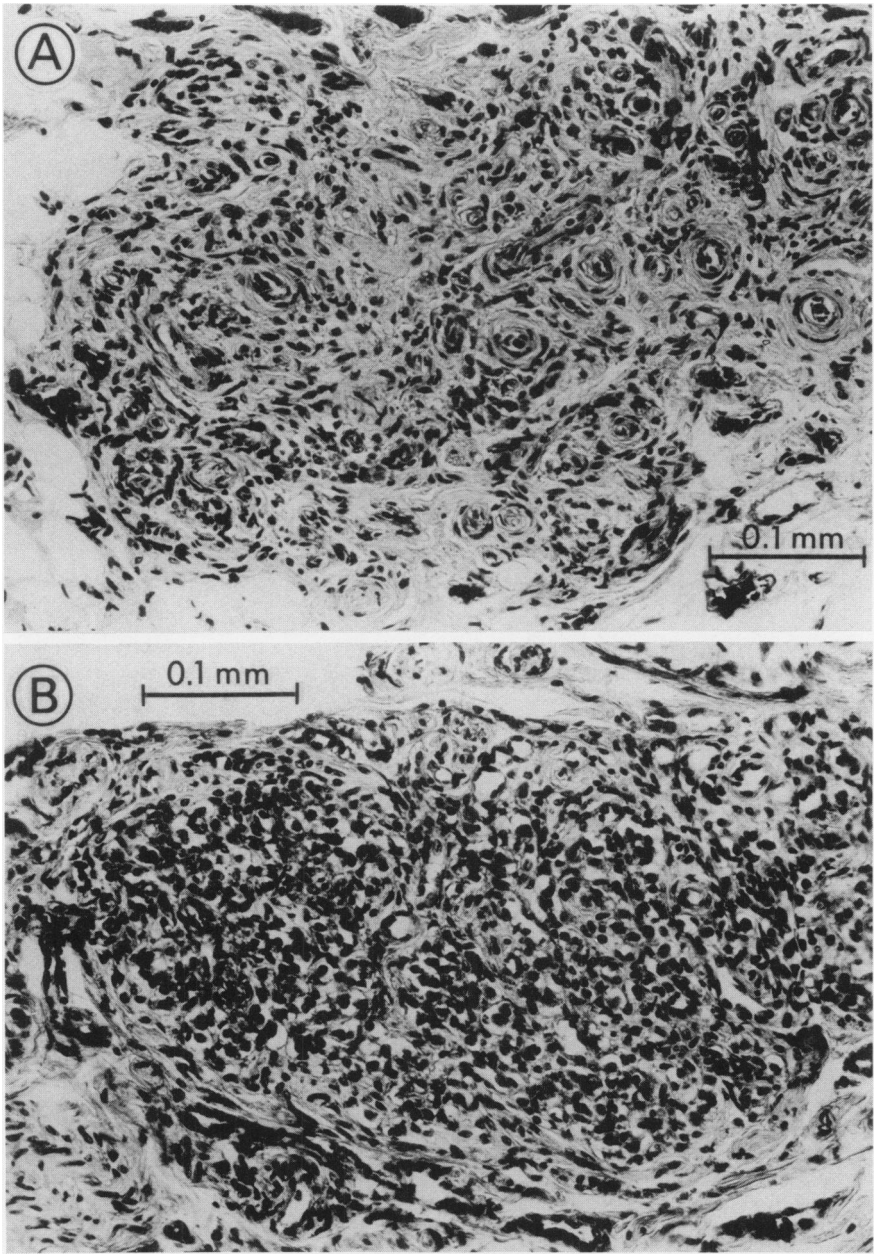

FIG. 1. Comparison of a human coronary chemoreceptor with minimal cellular infiltration (A) and one with extensive inflammation (B). Both are from hearts of victims of sudden death, female age 38 years in A and female age 12 years in B. Other photomicrographs from the same heart as A are shown in Figures 4 and 5. All photomicrographs are from sections prepared with the Goldner trichrome stain, and reference bars indicate magnification.

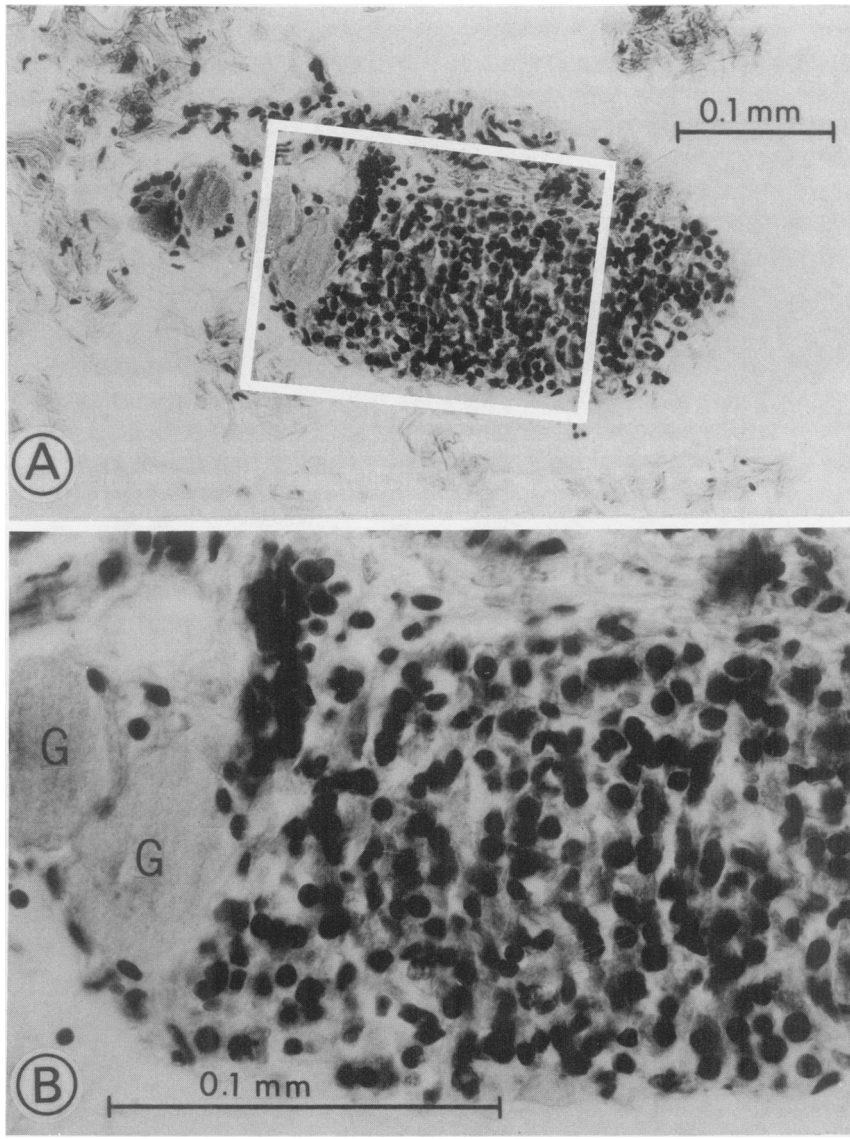

FIG. 2. Extensive inflammation and destruction are seen in this ganglion from the heart of 40 year old woman. Area boxed in A is seen at higher magnification in B, where G marks two ganglion cells. Note that the inflammation is confined to the ganglion.

process of repolarization both in the atria or ventricles. It is hardly surprising therefore that cardioneuropathies are readily demonstrable in the hearts of victims of sudden unexpected death (19–22).

Although chemodectomas or paragangliomas of various cervical and

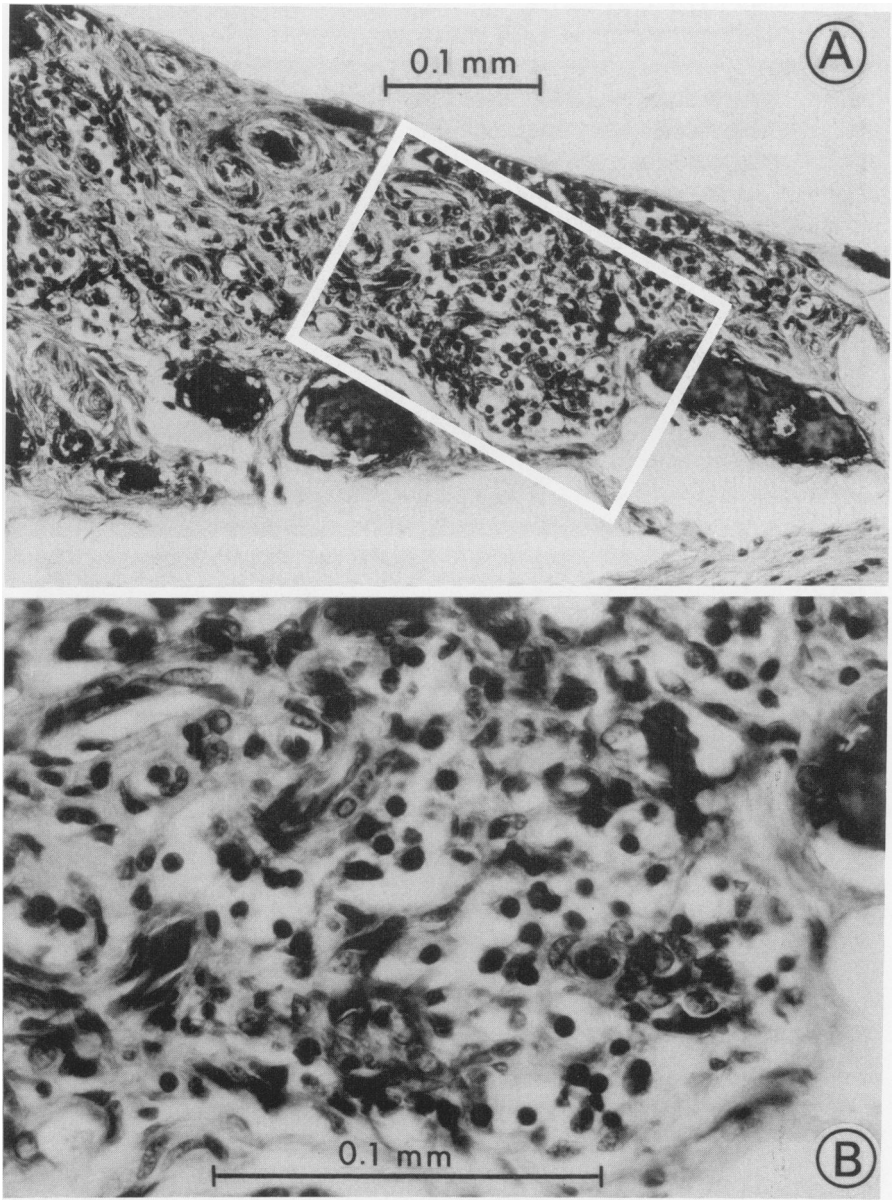

FIG. 3. A coronary chemoreceptor is depicted here containing inflammatory destruction similar to the ganglion shown in Figure 2 (same heart).

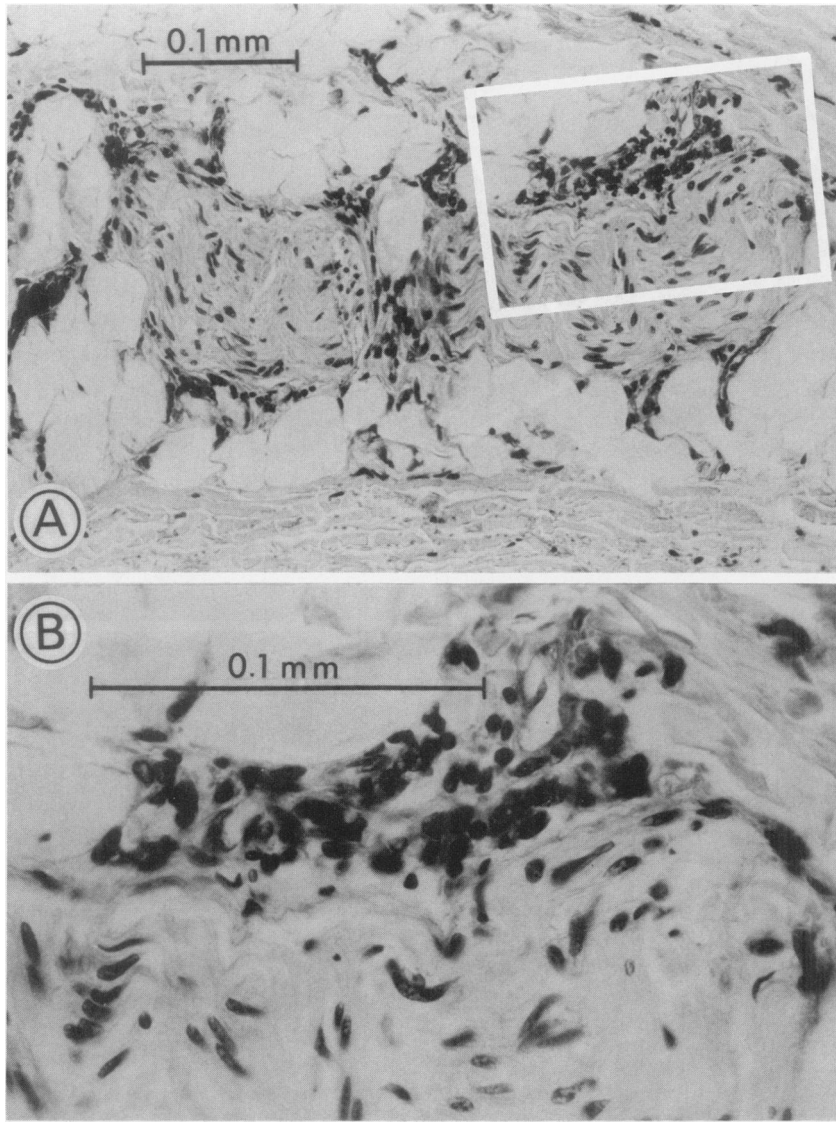

FIG. 4. Perineural inflammatory infiltration is shown here from the same heart as the coronary chemoreceptor in Figure 1A.

intrathoracic neuroreceptors (23–26), including the "aortic bodies" (27), have been described, to my knowledge no one has previously reported the histological appearance of the coronary chemoreceptor and its associated neighboring neural structures in the hearts of victims of sudden

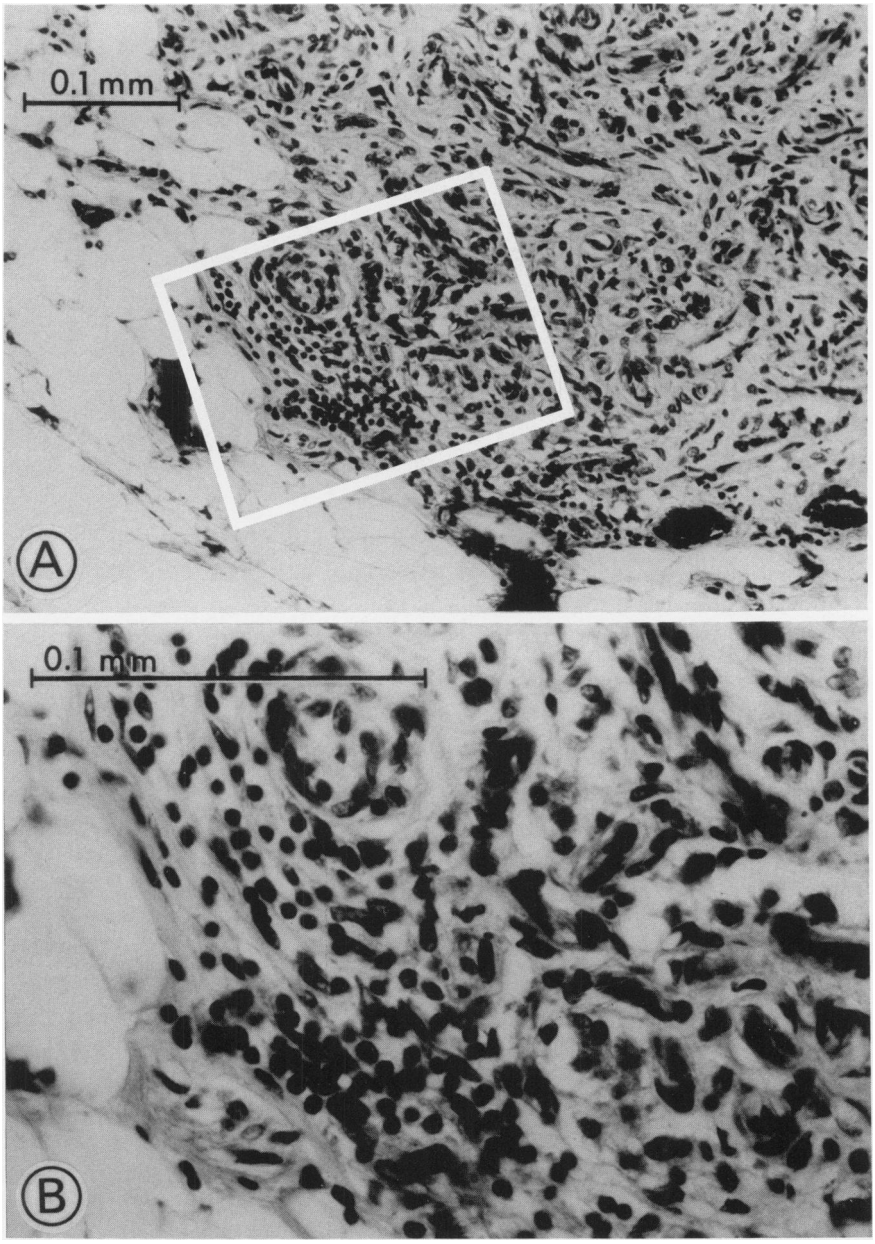

FIG. 5. Focal inflammation of a coronary chemoreceptor is boxed in A and seen at higher magnification in B. Same heart as Figures 1A and 4.

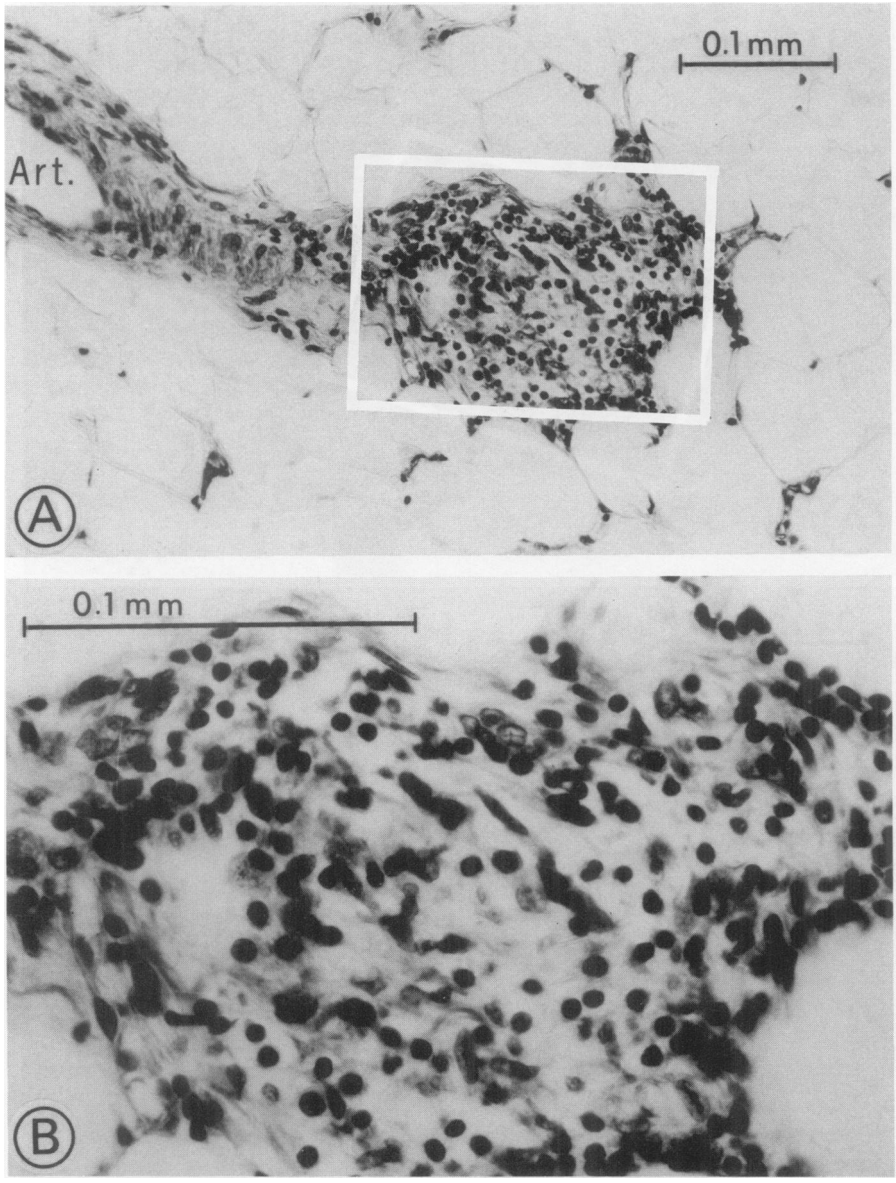

FIG. 6. Inflammatory destruction of a small coronary chemoreceptor is shown boxed in A and at higher magnification in B from the heart of a 39 year old man. Serial sections of this area demonstrated the chemoreceptor surrounding a small local artery (Art. in A).

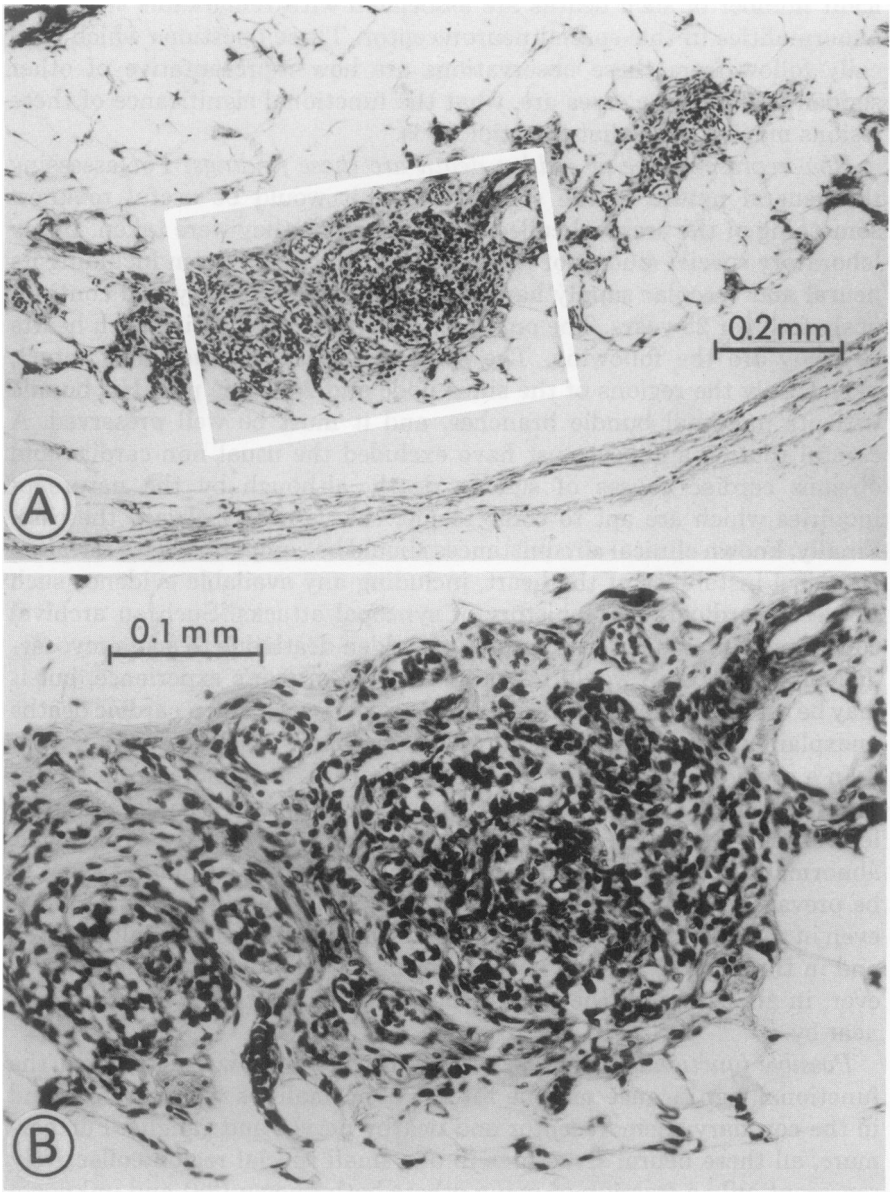

FIG. 7. Another coronary chemoreceptor from the same heart as in Figure 6 exhibits a focus of inflammatory destruction within the area boxed in A and shown at higher magnification B.

cardiac death. What is apparent from the present study is that a significant number of such deaths are associated with remarkable structural abnormalities in this special neuroreceptor. Three questions which logically follow from these observations are how representative of other sudden deaths these cases are, what the functional significance of these lesions may be, and what the etiology is.

How representative of sudden death are these findings? For assessing the general nature of the studied cases, it would be useful to know something of the archival collection from which they were taken. In my laboratory special studies of the cardiac conduction system including its neural and vascular supply have been conducted regularly and continuously for over 25 years. The only requirements for accepting such hearts to study are the following. The specimen must be reasonably intact, particularly the regions of the sinus node and AV node plus His bundle with its proximal bundle branches, and it must be well preserved. A careful routine autopsy must have excluded the usual non-cardiac and obvious cardiac causes of sudden death, although by the nature of inquiries which are apt to come to me, this is nearly always the case. Finally, known clinical circumstances should be compatible with terminal electrical instability of the heart, including any available evidence such as electrocardiograms or history of syncopal attacks. Such an archival collection contains fewer examples of sudden death due to acute myocardial infarction than would be found from a coroner's experience, but it may be even more representative of the universe of sudden cardiac deaths unexplained even after a careful routine autopsy.

In a previous histological study of the coronary chemoreceptor in five normal human hearts (5) there were no inflammatory or degenerative lesions. None of these was a case of sudden unexpected death. Thus, abnormalities of the kind found in the present study would not seem to be prevalent in all or most hearts examined postmortem. Furthermore, even in the present study the extent of chemoreceptor abnormality varied and in three of the sixteen hearts the chemoreceptor was normal. However, in all sixteen of the present hearts cardioneuropathy was present near by.

Possible functional signifiance. It is difficult to know exactly what the functional significance may be for the abnormalities which were found in the coronary chemoreceptor and nearby nerves and ganglia. Furthermore, all these neural structures in one small special region collectively represent only a fraction of many others both known (28) and unknown which are located elsewhere within the heart. Since there was no case in which abnormalities of the chemoreceptor occurred without other cardioneuropathy, it seems likely that the chemoreceptor, nerves and ganglia

are equally vulnerable and most apt to be involved jointly by whatever the cause may be.

How many and how severe or extensive do morphologic abnormalities in nerves, ganglia or glomera have to be to become functionally significant in the heart? There can be little doubt that neurally mediated distortions of cardiac electrical activity may take place with no demonstrable morphologic change at all. When structural abnormalities can be seen, there are no sure guides for interpreting whether they acted to stimulate or to distort or to eliminate the local neural activity, nor for estimating just what size a lesion must be in order to become functionally significant. Furthermore, since only one of each 30 eight-micron serial sections was examined, some lesions less than about 200 microns (0.2 mm) in maximal dimensions could have been missed even in the "normal" examples of chemoreceptor. Despite our present ignorance about these questions one can nevertheless deduce that the finding of any visible cardioneuropathy is at least worrisome.

The recognizable damage and destruction of either the chemoreceptor or its afferent or efferent pathways is probably gradual rather than abrupt, although the pace of progress may be episodic in nature. At some stage of the destruction, e.g., if it is inflammatory in nature, one could anticipate accentuated or increased activity, while at a later stage all activity would cease. Furthermore, either the chemoreceptor or nerves or ganglia may not only serve as the source of cardiogenic reflexes but also may represent simply a way station (or relay point) for reflexes originating elsewhere in the heart. For example, the region surrounding the main left coronary artery of the dog's heart which contains the chemoreceptor causing an excitatory influence upon the heart (hypertension, tachycardia [5]), is also precisely the narrowly funneled egress route for the von Bezold-Jarisch reflex (29) which originates from much of the left ventricular myocardium (30), and by contrast is inhibitory in nature (bradycardia, hypotension). In the dog, injection of xylocaine into the region around the main left coronary eliminates both the von Bezold-Jarisch reflex (29) and the cardiogenic hypertensive chemoreflex (5).

However, whether the events are excitatory or inhibitory and whether the studied region serves as a relay station, or an uninterrupted egress route or the actual originating source for cardiogenic reflexes, the anatomic abnormalities found can reasonably be suspected to have a significant influence upon most and perhaps all these events and processes. Additionally, some of the autonomic neural efferent signals to the heart from extracardiac receptors or from the brain may also traverse this same region, further compounding any possible functional significance of lesions found there. And, in ischemic heart disease where this cardi-

ogenic hypertensive chemoreflex has a putative role (16–18), the serotonin activating the reflex is probably released by locally aggregating platelets in the main left coronary artery, a formidably dangerous site for any thrombotic process.

Etiology of the abnormalities. At the present time one can rarely be certain of the etiology of most cardioneuropathies (19). Some considerations are obvious, such as either inhaled or ingested neurotoxic substances, or as a consequence of focal diseases known to damage nerves, such as amyloidosis or diabetes mellitus. These latter two and similar systemic diseases can usually be diagnosed from either clinical or anatomical evidence. Rare other cases may be the consequence of heritable neural degenerative diseases, which again should usually be suspected clinically. However, an undetermined but probably large percentage of all acquired cardioneuropathies are most logically attributable to either recent or ancient viral infections. Both the general recognition of this and the growing new evidence supporting a viral etiology are impressive. To cite only one such example, the varicella-zoster herpes virus is known to reside quietly or dormant within intrathoracic ganglia or other neural structures of many individuals for years or decades, only much later to become explosively and destructively active as shingles (31). What preserves the dormancy or terminates it to produce new activity is in most cases unknown, although patients receiving immunosuppressive therapy for cancer or organ transplantation are clearly at increased risk of activating a variety of dormant infections, including herpes varicella-zoster. Viral particles have been demonstrated in conjunction with cardioneuropathy in some victims of sudden cardiac death (32), but whether they were the true cause or functionally insignificant fellow travelers may be debated.

One may even ask if the abnormalities found in the present study of the chemoreceptor could be the consequence rather than the cause of sudden death. The agonal process of death may itself cause very powerful reflexes to come into play, including ones which perhaps so exhaust the responsible neural elements that they would be structually damaged. Such an explanation seems unlikely to be true because most of the observed inflammatory lesions could hardly have evolved in such a short time.

Epilogue. Whether or not it is possible to be certain of either the etiology or the exact functional significance of these neural lesions, one may logically deduce that they contributed in some way (e.g., by generating reflexes or distorting efferent signals or both) to electrical instability of the heart and, if the process was quick enough and powerful enough, to sudden death. In this respect the neural abnormalities may provide

the *coup de grace* if other conditions in the heart also favor electrical instability; but in rare cases they may themselves alone be sufficient cause.

Finally, one must consider these abnormalities of nerves, ganglia and glomera in the context of their location. Whereas a sural or sciatic neuropathy may be painful and even disabling, no question of survival is involved. For cardioneuropathies, on the other hand, one is dealing with a silent but powerful influence upon either the preservation or loss of cardiac electrical stability, including its possible lethal distortion. Whether we are being faced with a new disease, in the sense of its not previously being recognized, or only an unexplored special aspect of cardiac neuropathology remains to be determined. There is much yet to be done to clarify the prevalence, the etiology, functional significance and clinical assessment of these findings, but such knowledge should provide us with a new approach to understanding and possibly preventing sudden unexpected cardiac death.

SUMMARY

A coronary chemoreceptor and its neighboring nerves and ganglia were studied by serial sections of tissue taken from the hearts of sixteen victims of sudden unexpected death. Either focal or extensive inflammatory destruction was present in the chemoreceptors of 13 of the 16 hearts, and similar abnormalities of local nerves and ganglia were present in all 16 hearts. Since an identical coronary chemoreceptor in the dog has previously been shown to be the site of origin of a powerful reflex with major influence upon the electrical activity heart, the functional significance of the neural abnormalities found in these 16 human hearts may include important distortion of cardiac rhythm, conduction or repolarization. Future studies are needed to determine the prevalence of such lesions in the hearts of other victims of sudden death and among control subjects, as well as to determine the etiology of this special neuropathology of the heart.

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DISCUSSION

McCusick (Baltimore): All of us who have had an opportunity to see a cardiac transplant have certain questions that come to mind that we would be interested in having your response to. It's very dramatic when the heart of the recipient is placed into the stainless steel basin and the donor heart is put in place, completely denervated and seemingly the recipient makes out just fine without these cardioneuronal elements which you describe. How is this possible?

James: No problem at all, Victor. In a meeting about 10 years ago in Belgium, Dr. Ted Cooper who was then Director of the National Heart Institute, was charged with the same challenging question. It isn't the presence or absence of nerves which is the crucial factor. You're perfectly right that the transplanted heart is quite stable provided the source of the rhythm, for example, is not in a nerve-dependent area. The sinus node is less nerve-dependent for its automaticity and normal function than is the AV junction. One of the painful lessons early in the history of transplantation, in truth the very second transplant conducted, was that in which Kantrowitz excised the area of the sinus node, placed the heart in the chest of a child recipient and to his astonishment but of no surprise to those of us who have studied the question, the heart stopped in about three or four hours. The AV junction which virtually has to be the source of the rhythm in that kind of example is intensely dependent on its normal adrenergic neural input. But even more important there is a stage in between those of us who would hope we are normal with our nerves and those who have no nerves at all. That stage includes those who have some nerves only. Those people are the ones in whom heterogenity of neural influence becomes a destructive or unstabilizing influence. So to return to your initial point, yes, a heart that has its nerves removed is stable and will continue to beat normally provided the sinus node was retained. But those who only have some but not all of their nerves (upon which various hormonal and therapeutic pharmacologic influences are intermittently effective) will particularly be at jeopardy for the unstabilizing effect of focal neural degeneration.

Witham (Augusta): I'd like to congratulate Dr. James on his beautiful neurological paper. One obvious question, Tom. I'm sure you've examined a lot of controls, i.e., people who did not die of sudden cardiac death, and I wonder if there were any lesions that resembled these in those patients.

James: Thank you for your remarks. As I said when I was describing the technique, I don't think anyone is going to examine a lot of these because it takes a lot of work; it's a tedious process. I have had the opportunity to study five human examples of cardiac death who were not sudden death and in them the chemoreceptor appeared to be normal in all five.

Walker (Baltimore): Have you had an opportunity to look at this system in sudden infant death syndrome.

James: Yes. I've begun to do that, Gordon. There is some neural disease—cardioneu-

ropathy—in the hearts of victims of crib death. But there I believe the more suspect abnormality—abnormality may be the wrong term—the suspect focus for cardiac instability is the normal molding and shaping that occurs in the AV node and His bundle within the first few weeks and months of life. This normal postnatal morphogenesis is, I believe, the more logical focus for suspicion as a contributory cardiac cause in the crib death.